THE ACTION OF ACTH, CORTISONE AND PREDNISONE ON THE CONNECTIVE TISSUE OF NORMAL AND SCLERODERMIC HUMAN SKIN*

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The purpose of this paper is to describe the histological and histochemical modifications brought about in normal human connective tissue by the administration of ACTH, cortisone, hydrocortisone and prednisone and to compare these results with those obtained on the cutaneous connective tissue of sclerodermia and scleroedema adultorum treated with the same hormones.

Previous publications have described the inhibitory action of cortisone and other related steroids on the cells and intercellular substance of embryonic connective tissue in tissue culture (1, 2, 3) and on the hyperplastic connective tissue of various types of keloids (4, 5, 6). Similar actions of steroids have been demonstrated in granulation tissue (7, 8, 9).

Several months after the topical application of cortisone or similar compounds to the skin of the rat, there is an atrophy of the dermis with marked fusion of the collagenous fibers and bundles (10). On the other hand, parenteral administrations of high doses of desoxycorticosterone over long periods, does not seem to alter the dermis (11).

In patients with chronic sclerodermia, large doses of ACTH, cortisone and prednisone gave discrepant results. Atrophy of the collagenous fibers and bundles, with reduction in size of the fibrous zones, was evident after ACTH (electron microscope studies) (12) and after cortisone (light microscope) (13), but with prednisone no modifications were apparent after treatment (14). No data were reported on the modification induced with this hormone on the skin connective tissue in cases of scleroedema adultorum.

MATERIALS AND METHODS

Material

Normal adult skin was obtained from: (a) 6 normal human volunteers, and (b) 30 patients with localized diseases capable of improving temporarily with treatment with the hormones used in this study. In this group were 6 cases of Peyronie's disease, 4 cases of Dupuytren's disease, 10 cases of chronic eczema of the hands, 4 cases with chronic pretibial myxedema, and 6 cases of chronic asthma. The group of patients (12 cases) with sclerodermia comprised of 8 who had what is termed "Acrosclerosis", 2 who had the "Generalized Type" without acrosclerosis, and 2 who had the so-called "Scleroedema adultorum (Hardy-Buschke).

The following plan for treatment was adopted:

Normal adult skin. The 6 adult volunteers were treated twice daily with a local application of a 1% hydrocortisone ointment for a period of one to eight months.

The remaining 30 adults were divided into three groups:

Group "A" (12 cases), received 20 mg. daily, intravenously of ACTH during one month. After discontinuing treatment for two months, the patients were kept for one month on 20 mg. daily oral prednisone.

Group "B" (14 cases), was treated with ACTH in the same manner as group "A", but after discontinuing treatment for two months was given cortisone orally for one month in the following way: 200 mg. daily during the first week, 100 mg. daily during the second and third, and 75 mg. daily during the last week.

Group "C (4 cases), received smaller doses of ACTH, 5 mg. daily for 8 weeks intravenously. After discontinuing treatment for one month, two members of this group were treated with 10 mg. daily of prednisone for 8 weeks orally, and the two remaining received 75 mg. daily of cortisone for 8 weeks orally.

Sclerodermic skin (12 cases). This group was started on intravenous injections of 20 mg. daily of ACTH for one month; after discontinuing treatment for two months, one half of the group received oral cortisone for 4 weeks (200 mg. daily the first weeks, 100 mg. daily during the second and third, and 75 mg. daily during the fourth); the other half received oral prednisone (30 mg. daily the first two weeks, and 20 mg. daily for the last two). The group was retreated at intervals of two or three months, with each of the three schedules.

Biopsies

All biopsy specimens were removed after anesthetizing the skin with a Ghyl-Chloride spray.

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Normal skin. A control biopsy specimen was taken from all subjects 5 days before commencing the treatment. A small section was removed from the upper-third anteroexternal zone of the thigh. The specimens were removed after treatment in all groups a distance away from the control biopsy. Three biopsies were taken: one on the eighth day, the second on the fifteenth day, and third at the end of the treatment. Group "A" (treated locally with hydrocortisone) also had three specimens taken before and during treatment, and on the second, fourth and eighth month of treatment. In certain selected cases, from all groups, still another specimen was taken one to two months after ending the treatments.

Sclerodermic skin. This group, as in the cases of normal skin, also had a previous biopsy specimen taken from the skin of the thigh, as well as a specimen of their pathological skin from the dorsum of the finger, forearm or the abdomen. After treatment, specimens were taken on the eighth, fifteenth, and last day of treatment. In the majority of cases another biopsy specimen was made one to two months after suspending all treatment.

Technic Employed

All pieces of skin were placed immediately in Bouin or Zenker's fluids and in 10% formalin. After paraffin embedding, sections from each specimen were treated with the following technics: (1) For the overall morphology they were stained with hematoxylin and eosin and by Heidenhain's Azan method; (2) for collagenous and reticular fibers the silver technique of del Rio Hortega; (3) Weigert's method for demonstrating elastic fibers; (4) nucleoproteins and mucopolysaccharides were stained respectively with 0.25% toluidin blue at pH 3.5 and 6; specificity of the basophilia and metachromasia was controlled by incubating the section with hyaluronidase (30 u.t. per cc, pH 6.0 at 37° C for 12 hours) and with perchloric acid (4% at 60° C for 10 min.); (5) the PAS reaction was used to demonstrate the basement membrane and reticular fibers; the specificity of this technic for glycogen and glycoprotein was tested by incubating sections in ptyalin (37° C, 2 hours) and methanol-chloroform (60° C, 3 hours); (6) del Rio Hortega's panoptic silver-impregnation technique was used to differentiate the cell types.

RESULTS

The results obtained with the three hormones in normal and pathological human skin were quite constant, and very similar as regards the qualitative modifications in the connective tissue.

TABLE 1

Histological and histochemical modifications of human normal skin after administration of prednisone, ACTH and cortisone

Skin (Structures)	Previous Biopsy	2 Weeks After Hormone Administration	4 Weeks After Hormone Administration
Epithelium	Normal	No changes	Slightly atrophic, cellular vacuolization
Basal membrane	Well marked, continuous	Slightly thinner	Still thinner and discontinuous
Collagen fibers	Criss crossed, homogeneous highly eosinophilic	Separate, thinner and parallel to each other	Atrophic, dissociated and with lessened eosinophilia
Reticular fibres	Abundant, densely knit	Separate and loosely knit	Thin and dispersed
Elastic fibers	Abundant, long	Short and slightly fragmented	Fragmented, elliptic and basophilic
Mucopolysaccharides	In the chorium papillae	No change	Disappeared
Fibroblasts	Numerous. Many appear juvenile with cytoplasmic nucleoprotein granules	No change	Less numerous. Partly atrophic and devoid of nucleoproteins
Mast-cells	Variable shape, exceedingly granular	No change	Partly atrophic and degranulated
Arterioles and capillaries	Reticular fibres in a fine and closely knit pattern in the wall	No change	Some with a very loosely knit reticular net

TABLE 2

Histological and histochemical modifications of sclerodermic skin after administration of prednisone, ACTH and cortisone

Skin (structures)	Acrosclerosis and Diffuse Sclerodermia		Sclerodermia Adultorum (Hardy-Buschke)	
	Before hormone administration	After hormone administration	Before hormone administration	After hormone administration
Epithelium	Normal cellular layer with hyperkeratosis	No change	Normal	No change
Basement membrane	Thickened. Dense mesh of reticular fibres	No change	Thickened. Dense mesh of reticular fibres	No change
Collagen fibres and bundles	Dense and in part fused hyalinized zones	Atrophic. Dissociated. Reduction of hyaline zones	Hypertrophic and hyperplastic. Dense and interwoven	Parallel. Atrophic and dissociated
Reticular fibres	Scarce in the superficial and middle layers of the chorium	No change	Thin and scarce in the superficial and deep stratae of the chorium	No change
Elastic fibres	Short, thick and scarce in the middle layer of the chorium. Thin and long in the superficial layer	Thinner and fragmented	Short, thick and scarce throughout the chorium	Thin, fragmented and scarce
Mucopolysaccharides	Demonstrable in the papillaric chorium	Absent	Slight amount	Absent
Fibroblasts	Moderate number. The majority are of the adult type, with few cytoplasmic nucleoprotein granules	In part atrophic, with nuclear pycnosis and without cytoplasmic nucleoproteins	Hypertrophic and hyperplastic. Numerous nucleoprotein granules	Reduced in number. In part atrophic and without nucleoproteins
Mast cells	Scarce. All are distributed perivascularly	A few are vacuolated and degranulated	Usual number and normal appearance	Partly degranulated and vacuolated
Arterioles and capillaries	Partial sclerosis	No change	Slight sclerosis of some of the arterioles and capillaries	No change

The intensity of the histological modifications does not seem to depend on the route of administration, but variations in doses do produce different results. Comparison of the biopsy studies (Figs. 1 and 2), shows that at 4 week treatment skin was affected far more by prednisone (Figs. 3 to 16) than by ACTH, and least of all by cortisone. Changes caused by local applications of hydrocortisone ointment in normal skin did not reach the magnitude of those produced by the other hormones, and the changes took place more slowly, being perceptible only after two months treatment; they were more evident after eight months (Figs. 17 to 20). Two months after the suspension of all treatments. there was total remission of all histological modifications.

The histological modifications were more pronounced in the deep and middle parts (Figs. 3 to 6) of the corium in those cases treated by oral or parenteral routes. In such cases it involved not only different components of connective tissues (Figs. 10 to 16), but also the basal membrane (Figs. 7, 8, 9). The changes in subjects treated by local application were most marked in the superficial layer and decreased gradually towards the deeper parts, perhaps reflecting the rate of diffusion of the hormones.

In Table 1 is a summary of the results obtained by treating normal adult human skin with ACTH, prednisone and cortisone for 2 to 4 weeks. Details of these cases treated with smaller doses are not included because the results were similar but less pronounced.

Table 2 shows the details of the results obtained in sclerodermic skin. The histological and histochemical results before and after treatment were, in general, equal in cases of scleroedema adultorum (Figs. 21 to 28) and in cases of acrosclerosis and of diffuse scleroderma (Figs. 29 to 36).

Thus, before treatment the connective tissue, when in the chronic stage of these diseases, shows a tendency towards developing fibrosis and hyalinized zones, either together or separate. This occurs preferentially in the middle and deep layers of the corium. Some of the arterioles also show hyalinization of the intima, with mononuclear infiltration. In scleroedema adultorum a true hypertrophy and hyperplasia of the collagenous bundles and fibers occurs, separated by large interstices; this is accompanied by an increase in the number of young fibroblasts. The vascular changes and the cellular infiltrates are minimal.

DISCUSSION

Morphological and histochemical studies show that ACTH, cortisone and prednisone produce similar modifications in the connective tissue of skin, both normal and sclerodermic.

Serial biopsy studies from each patient show that the modifications can be seen after treatment for 8 days and progress until the fourth week. This takes place as long as the doses given are large and sustained. Smaller doses, even though administered for longer periods of time up to two months, produce only slight changes. With the higher doses used the patients showed moderate signs of hypercorticalism at the end of 4 weeks treatment. These signs disappeared after the withdrawal of the hormones. The comparative value of ACTH, prednisone and cortisone was established by treating each case successively with the three compounds. During equal periods of medication, orally administered prednisone produced more intense and constant results than did intravenous ACTH, and oral cortisone. Yet, the variable sensitivity of individuals to the hormones, the corticoadrenal reserve, and the doses used should be considered (15).

The results obtained by local applications are almost identical to those brought about by systemic therapy. This gives strength to the hypothesis that adrenal corticoids have a direct action on the connective tissue.

All changes are reversible, and the connective tissue regains its normal appearance when the administration of the hormones is stopped.

The alterations which followed administration of corticoids was frankly involutive, and effected both cells and intercellular substance. Even though during the first weeks changes were more evident in the intercellular substances, as treatment progresses the action became noticeable in the cells. At first the collagenous fibers and bundles begin to atrophy and to lose their interwoven appearance; the elastic fibers thin out and become fragmented. At this stage the mucopolysaccharides, the reticular fibers, the basement membrane and the cellular components remain apparently unchanged. Later the mucopolysaccharides disappeared, the three types of fibers become dissociated, and even the basement membrane is thinner and loses both glycoproteins and reticular fibers. Some of the fibroblasts are

smaller, fusiform and show nuclear pycnosis and lose the cytoplasmic basophil granules. Some of the mast cells lose their granules and become vacuolated. Other authors (16, 17) have described similar alterations in mast cells, as a direct action of adrenal corticoids.

In some cases there is a partial atrophy of the epidermis and of the erector pili muscles; at the same time the reticular net of the smaller arterioles was lax and disperse.

In summary, the atrophy of normal cutaneous connective tissue after the administration of ACTH and glycocorticoids is qualitatively similar to that produced by the same hormones in the connective tissue of chick embryo (18) and in the hyperplastic connective tissues of wounds and keloids.

In cases of sclerodermia the hormones bring about a partial atrophy of the fibrosis, a reduction of the thickness of the elastic fibrils, and no changes in the density of the basement membrane. The slight effect on the zones of fibrohyalinosis is explainable by its degenerative nature (19).

It is not strange that the hyperplasia and hypertrophy of cells and collagenous fibers, which represent genuine fibroplasia characteristic of a scleroedema adultorum, should be inhibited and atrophied. In these cases, as in normal ones, one of the earliest changes is a loss of the intermeshing fibrillar components of the middle and deep parts of the corium.

In sclerodermia and more notably in scleroedema, the hormones have a simultaneous and parallel action on the cells and intercellular substance. Fibroblasts and mast cells become atrophic and lose their granulations, although somewhat less than they do in normal skin. On the other hand, no changes were observed in the epidermis, cutaneous adnexa, and hyalinized arteriolar walls, other than those that were seen in normal skins under similar conditions.

Perhaps all these actions can be better explained by the direct antianabolic action of these hormones on the connective tissue, than by the lack of protein supply to the tissue, as a consequence of a generalized accelerated protein catabolism (20). This hypothesis could explain the nature of the changes produced in growing connective tissues, such as that of the embryo, granulation tissue and keloids. The aetion of the hormones in these cases may be more marked since the tissues are in an intense anabolic stage.

Even though adult connective tissue has a slow metabolic rhythm (radioisotopic studies) in both its fibrillar (21) and mucopolysaccharide components (22), these hormones have an antianabolic action on it. It has been shown that hydrocortisone decreases the amount of mucopolysaccharides content of connective tissue in skin of adult rats (23).

These reasons give some validity to the observation that the effect of these hormones on sclerodermic tissue is less intense than on normal ones, for this is a tissue with fibrohyalin, involutive zones, and has a lessened metabolic turnover.

The evidence presented here also strengthens the theory of the interdependence of cells and intercellular substance in both normal and pathological connective tissues (24).

SUMMARY

Histological and histochemical studies were made on the connective tissue of the skin in normal subjects and in cases of sclerodermia and scleroedema adultorum, during and after treatment with ACTH, cortisone and prednisone administered parentally or topically with an ointment of hydrocortisone.

Normal skin. (1) There is a progressive atrophy of the collagen bundles and fibers, which lose their normal intercrossing and appear thinner and dissociated; (2) the reticular and the elastic fibers appear thinner and fragmented; (3) the interfibrillar mucopolysaccharides disappear; (4) the basement membrane appears thinner, discontinuous, and the network of reticular fibers presents a loose arrangement; the PAS reaction in the basement membrane becomes weaker; (5) many of the fibroblasts lose their extensions, their nuclei become pycnotic and the nucleoprotein granules disappeared from the cytoplasm. Some of the mast cells lose their granules and attain vacuoles in their cytoplasm. The reticular fibers in the walls of the arterioles seem lax and dispersed.

Skin lesions of *sclerodermia* and *scleroedema adultorum*: (1) There is an atrophy and dissociation of the hypertrophied collagen bundles and fibers and of the elastic fibers; (2) reduction of the zones of hyalinization which appears partially disintegrated; (3) the little mucopolysaccharide present in the papillary corium disappeared; (4) the glycoprotein substance and the reticular fibers of the basal membrane and the

hyalinized arterioles show no changes; (5) fibroblasts seem less hypertrophied and lose their cytoplasmic nucleoproteins; some of the mast cells lose their granules and attain vacuoles.

In all cases the changes were progressive and they reached their peak about 4 weeks after treatment. They seemed to be more marked with prednisone than with ACTH or with cortisone. The changes appeared to be reversible, as the skin became normal again when the administration of these hormones was stopped.

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REFERENCES

1. Mancini, R. E. and Lustig,. E S. de: Acción de los esteroides adrenales sobre los mucopolisacaridos y fibras colágenas en cultivos de fibroblastos. Rev. Soc. Arg. Biol., **27:** 86, 1951.
2. Corman, C.: Selective damage to fibroblasts by desoxycorticosterone in cultures of mixed tissues. Science, **113:** 37, 1951.
3. Geiger, R. S., Dingwall, J. A. and Andrus, W. de W.: Effect of cortisone on growth of adult and embryonic tissue "in vitro". Am. J. M. Sc., **231:** 427, 1956.
4. Mancini, R. E.: Inhibición de la fibroplasia del queloide por acción local de hidrocortisona. Rev. Soc. Arg. Biol., **30:** 107, 1954.
5. Mancini, R. E. and Stringa, S. G.: Acción local de la hidrocortisona en diferentes variedades de queloides. Rev. arg. Endocrinol Metab. **1:** 241, 1955.
6. Asboe-Hansen, G., Bredhagen, H. and Zachariae, L.: Treatment of keloids with topical injections of hydrocortisone acetate. Arch. Dermat. & Syph., **73:** 101, 1956.
7. Taubenhaus, M.: The influence of cortisone upon granulation tissue and its synergism and antagonism to other hormones. Ann. New York Acad. Sc., **56:** 666, 1953.
8. Williamson, M. B.: The healing of wounds. A symposium on recent trends and studies, p. 113. McGraw-Hill Book Oompany, New York, Toronto, London, 1957.
9. De Brux, J. et Duboistesselin, R.: Modifications histologiques et histoquimiques du tissu conjonctif sous l'influence de différentes actions hormonales. Presse Médicale, **61:** 600, 1953.
10. Castor, C. W. and Baker, B. L.: The action of adrenocortical steroids on epidermis and connective tissue of the skin. Endocrinology, **47:** 234, 1950.
11. Pirani, C. L., Stepto, R. C. and Sutherland, K.: Desoxycorticosterone acetate and wound healing. J. Exper. Med., **93:** 217, 1951.
12. Lillo, M.: Electron microscopy observations on the subject of collagen disease. Acta. med. Scand., suppl. **311:** 825, 1956.
13. Taubenhaus, M. and Lov, M.: Clinical and histological observations on a case of scleroderma treated with cortisone. Arch. Int. Med., **67:** 583, 1951.
14. Rodnan, G. P., Black, R. L., Jay Bollet, A. and Bunin, J. J.: Observations on the use of prednisone in patients with progressive systemic sclerosis (diffuse scleroderma). Ann. Int. Med., **44:** 16, 1956.
15. Mancini, R. E., Stringa, S. G. y Cánepa, L.: Estudio clínico, humoral e histológico de la acción del ACTH en esclerodermias generalizadas. Rev. Arg. Endocrinol. Metab., Supl. **1:** 1, 1957.
16. Cavallero, S. and Braccini, C.: Effect of cortisone on the mast cells of the rat. Proc. Soc. Exper. Biol. & Med., **78:** 141, 1951.
17. Asboe-Hansen, C.: Connective tissue. Conf. J. Macy Found., p. 123, 1954.
18. Mancini, R. E., Lustig, E. S. de and Pogo, B.: Cytochemical and radioautographic studies on the effect of hydrocortisone on the embryonic connective tissue "in vivo" and "in vitro". In press.
19. Seville, R. H.: Sclerodermia dermatomyositis (with electronmicrographs). Brit. J. Dermat., **64:** 467, 1952.
20. Asling, C. W., Reinhardt, W. O. and Li, C. H.: Effects of adrenocorticotropic hormone on body growth, visceral proportions and white blood cell counts of normal and hypophysectomized male rats. Endocrinology, **48:** 534, 1951.
21. Robertson, W. and Schwartz, B.: Ascorbic acid and the formation of collagen. J. Biol. Chem., **201:** 689, 1953.
22. Boström, H.: On the sulphate exchange of sulpho-mucopolysaccharids; connective tissue in health and disease, p. 47. E. Munskaard, Copenhague, 1954.
23. Sobel, H. and Marmorston, J.: The effect of cortisone on the collagen and hexosamine content of the skin and femurs of one year old rats. Endocrinology, **55:** 21, 1954.
24. Mancini, R. E.: Fisiopatología del tejido conectivo. Rev. Asoc. Med. Arg., **67:** 302, 1953.

PLATE 1

Fig. 1. Biopsy of skin from normal subject before treatment with prednisone. Normal connective tissue in all layers. H.-E. × 96.

Fig. 2. Area of the middle chorion corresponding to fig. 1 at high magnification. H.-E. × 365.

Fig. 3. Biopsy of skin from the same case two weeks after treatment with prednisone. Disruption of the normal architecture of collagen in the middle chorion. H.-E × 96.

Fig. 4. Area of the middle chorion corresponding to fig. 2 at high magnification. H.-E. × 365.

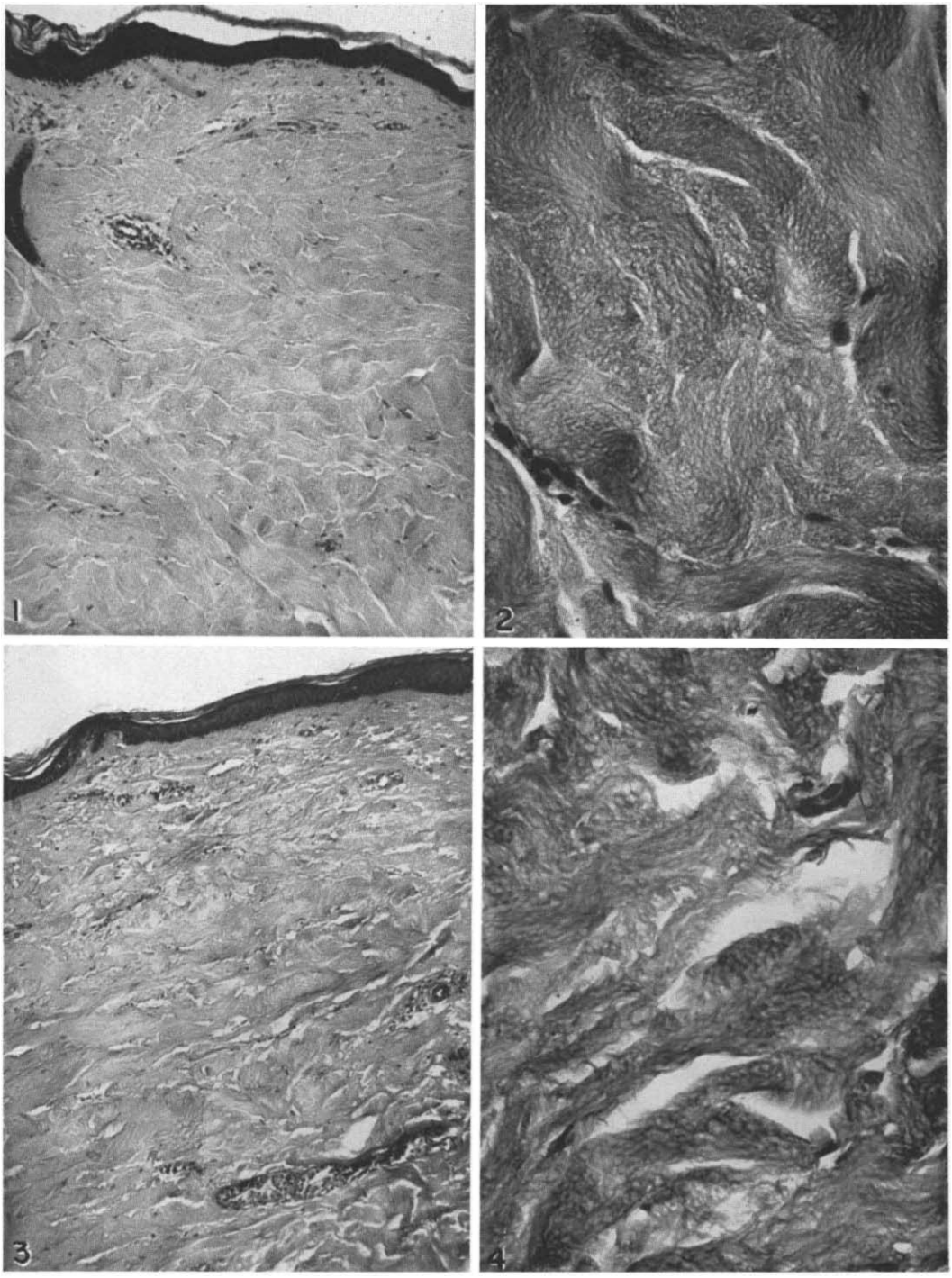


PLATE 1

PLATE 1

FIG. 5. Biopsy of skin from the same subject four weeks after treatment with prednisone. Separation and dissociation of collagen bundles in the middle chorion. H.-E. × 96.

FIG. 6. Area of the middle chorion corresponding to fig. 5 at high magnification. H.-E. × 365.

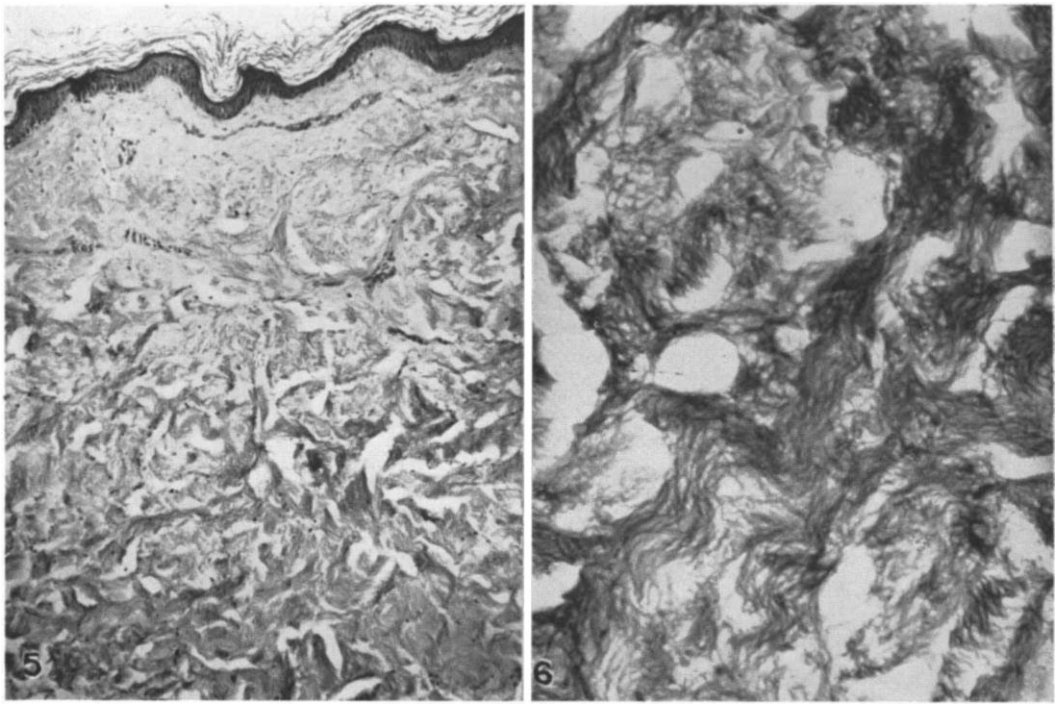
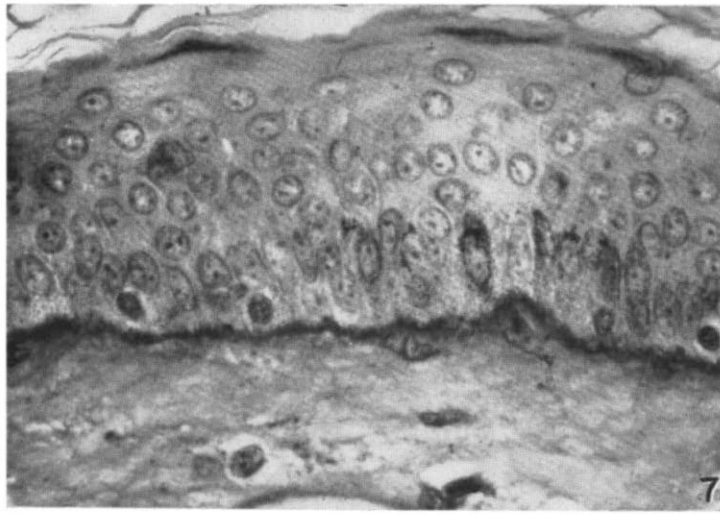
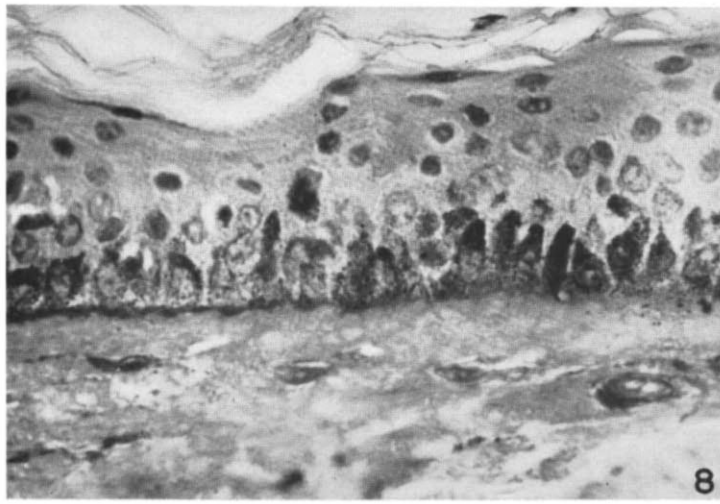


PLATE 1

PLATE 2

FIG. 7. Basal membrane of skin corresponding to fig. 1 (PAS-hematoxylin method). × 630.
FIG. 8. Basal membrane of skin corresponding to fig. 3. It is thinner in some areas than that of fig. 7. (PAS method) × 630.
FIG. 9. Basal membrane of skin corresponding to fig. 5. Partial atrophy in some areas.





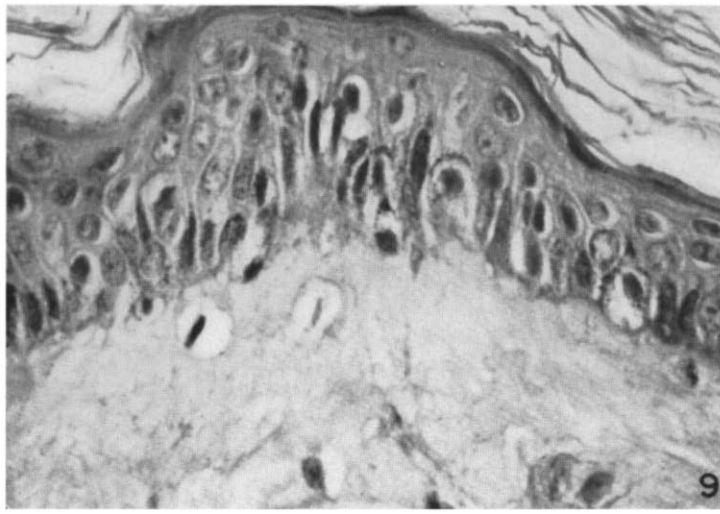


PLATE 2

PLATE 2

FIG. 10. Elastic fibers of middle chorion of skin corresponding to fig. 1. Orcein technic. × 378.

FIG. 11. Elastic fibers of middle chorion of skin corresponding to fig. 3. Fragmentation of elastic fibers. Orcein technic. × 378.

FIG. 12. Elastic fibers of middle chorion of skin corresponding to fig. 5. Atrophy of elastic fibers. Orcein technic. × 378.

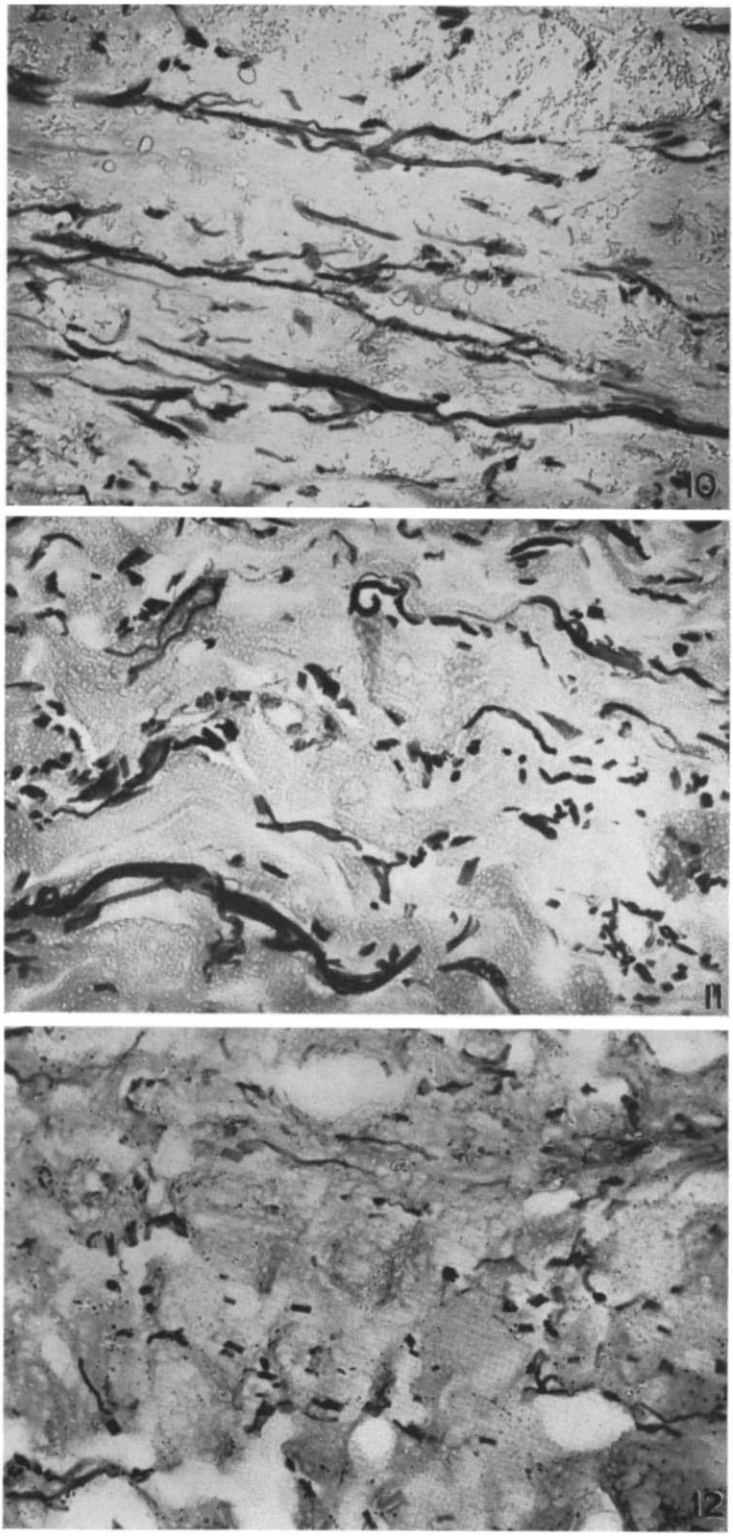


PLATE 2

PLATE 3

FIG. 13. Fibroblasts of the middle chorium of skin corresponding to fig. 1. Basophilic stain of nucleolus and some granules in the cytoplasm. Toluidine blue (ph. 3.5) × 1479.

FIG. 14. Fibroblasts of the middle chorium of skin corresponding to fig. 5. Picnotic nuclei and atrophy of cytoplasm. Toluidine blue (ph. 3.5) × 1479.

FIG. 15. Mast cell of the chorium of skin corresponding to fig. 1. Metachromatic granules in the cytoplasm. Toluidine blue (ph. 5) × 1479.

FIG. 16. Mast cell of the chorium of skin corresponding to fig. 5. Part of them showing vacuolization and degranulation. Toluidine blue (ph. 5) × 1479.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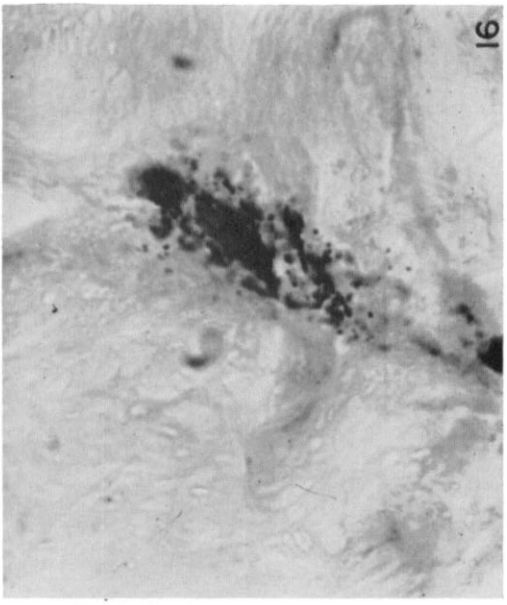
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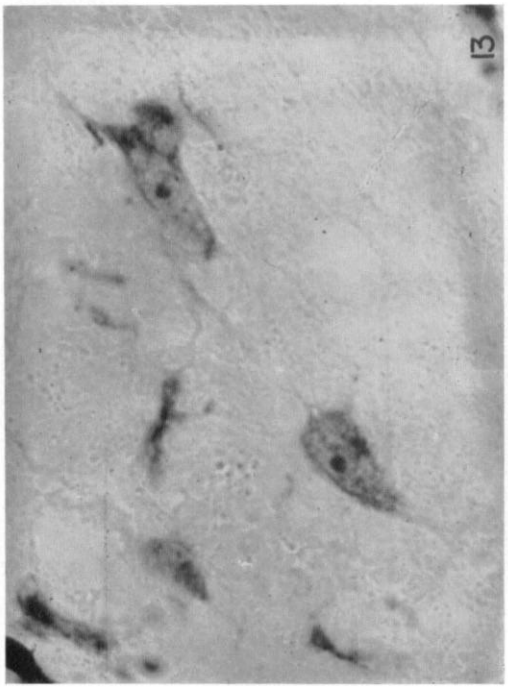
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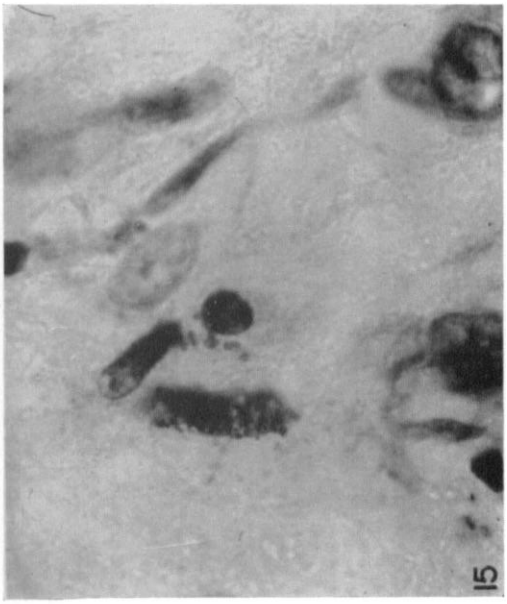
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PLATE 4

FIG. 17. Superficial chorium of normal skin before local treatment. Hematoxylin-eosin. × 261.
FIG. 18. Middle chorium of the same case. Hematoxylin-eosine. × 261.
FIG. 19. Superficial chorium corresponding to the preceding case after six months of topically applied hydrocortisone ointment. Dissotiation of collagen fibers and bundles and partial atrophy of fibroblasts. Hematoxylin-eosine. × 261.
FIG. 20. Middle chorium of the preceding case after same treatment. Slight dissotiation of collagen bundles. Hematoxylin-eosin. × 261.

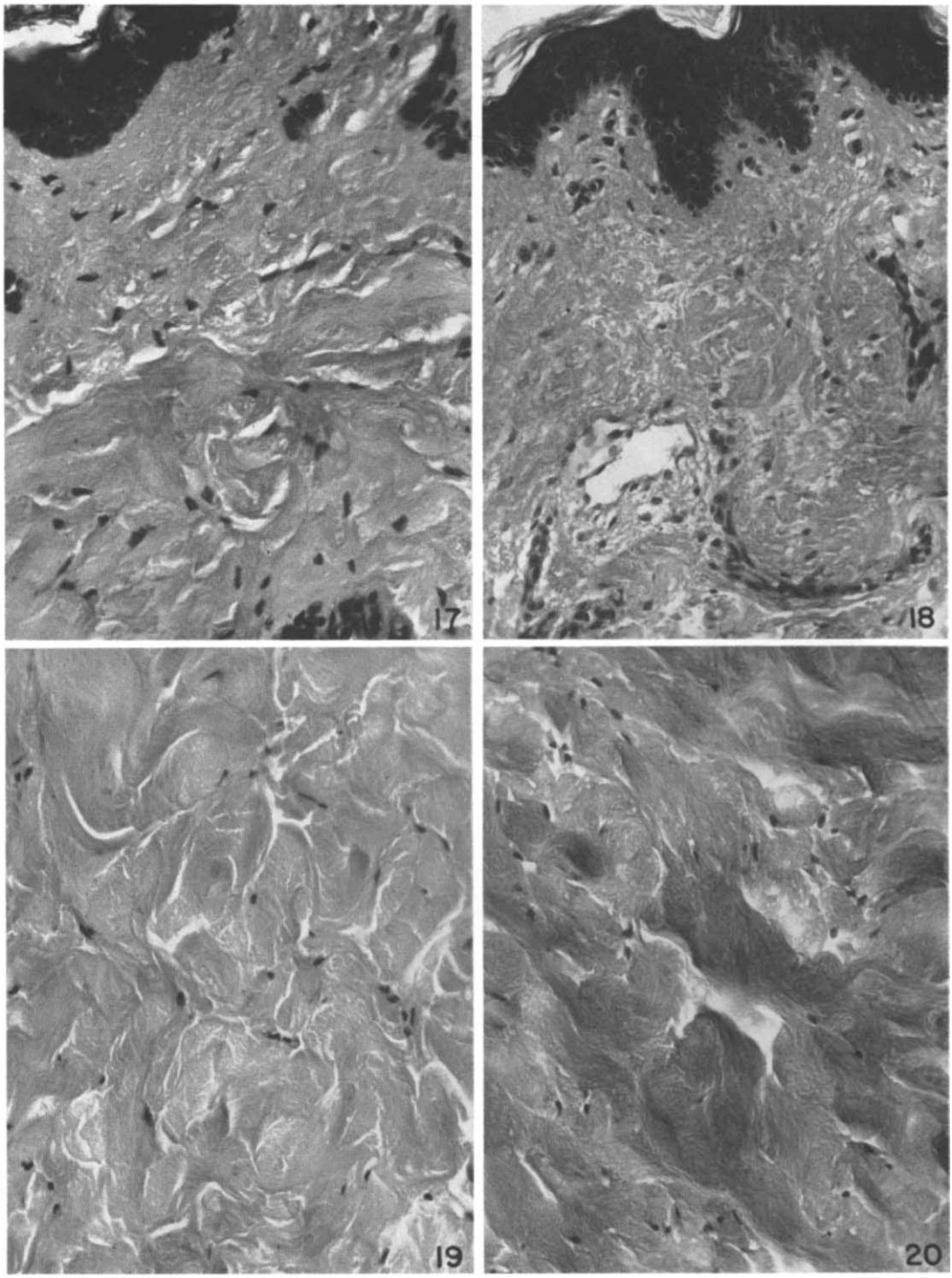


PLATE 4

PLATE 5

FIG. 21. Skin of "scleroedema adultorum" before treatment with prednisone. Marked fibroplasia, thick and interwoven collagen bundles and hyperplasia of juvenile fibroblasts. Perivascular infiltration of mononuclear cells. Hematoxylin-eosine. × 96.

FIG. 22. Middle chorium of the preceding case at high magnification. Hematoxylin-eosin. × 331.

FIG. 23. Same case after four week treatment with prednisone (30 mg daily). Disruption and separation of collagen bundles, and reduction of mononuclear cells around vessels. Hematoxylin-eosin. × 96.

FIG. 24. Middle chorium of the preceding case after treatment at high magnification. Dissotiation on atrophy of hypertrophic collagen bundles. Hematoxylin-eosine. × 331.

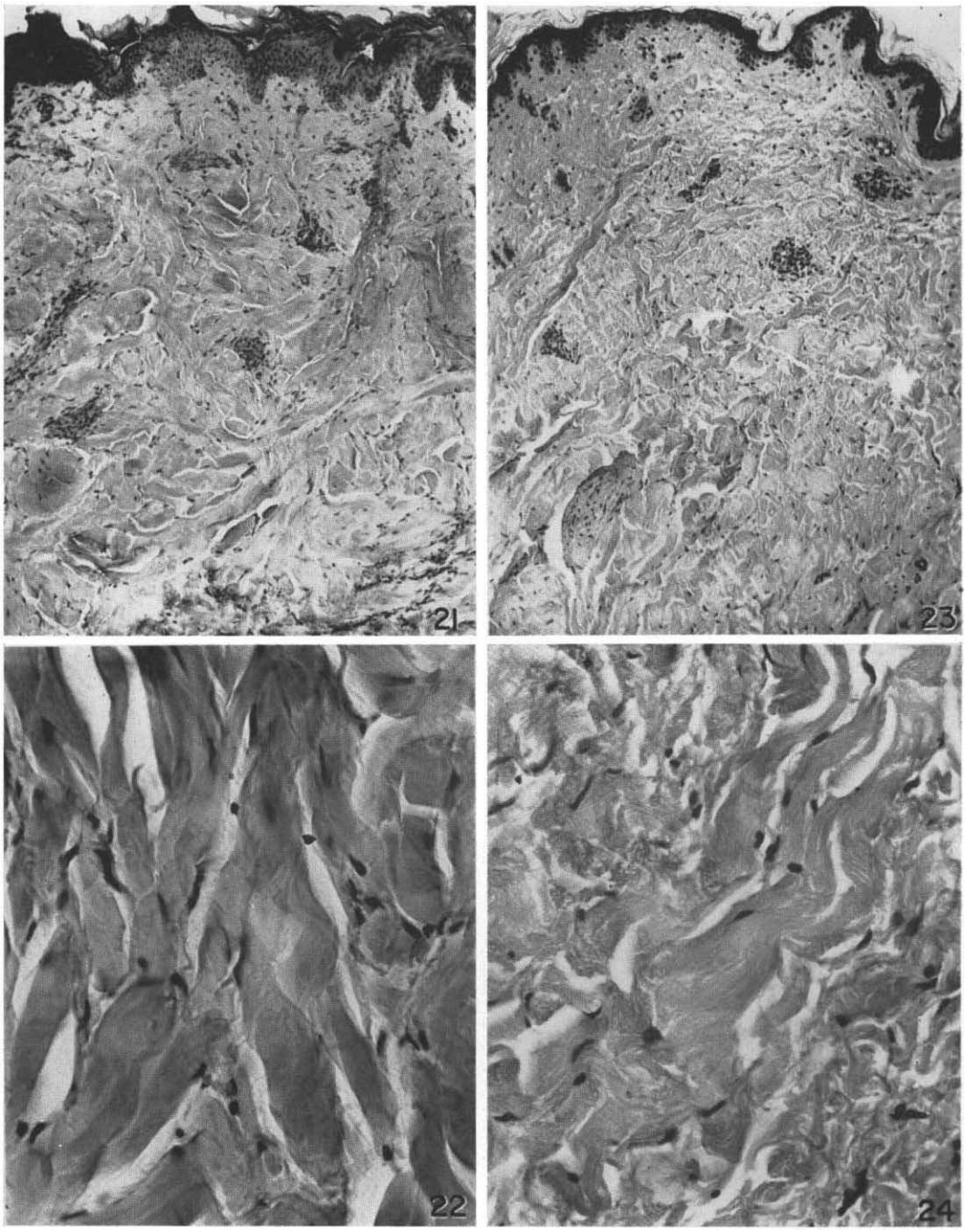


PLATE 5

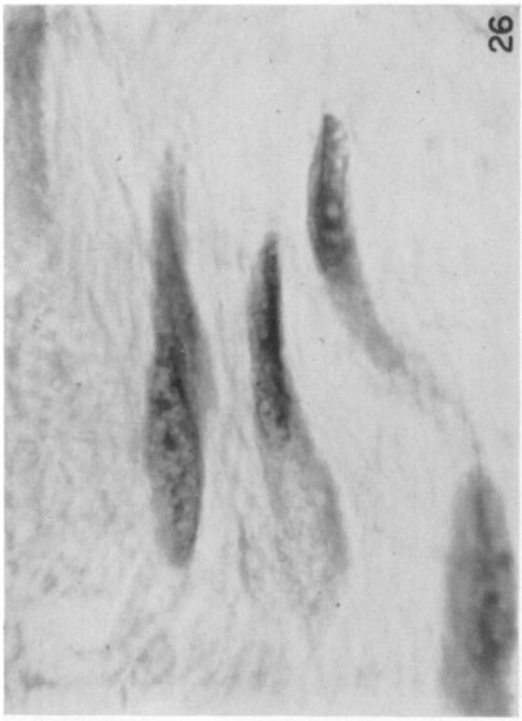
PLATE 6

FIG. 25. Hypertrophic juvenile fibroblast corresponding to skin of scleroedema adultorum before treatment. Large nucleus with nucleolus and marked basophilia of cytoplasm. Toluidine blue (ph. 3.5) × 1479.

FIG. 26. Atrophic fibroblasts of the same case after treatment with prednisone. Toluidine blue (ph. 3.5) × 1479.

FIG. 27. Thick elastic fibers of the preceding case before treatment with prednisone. Orcein technic. × 365.

FIG. 28. Fragmented elastic fibers of the same case after treatment. Orcein technic. × 365.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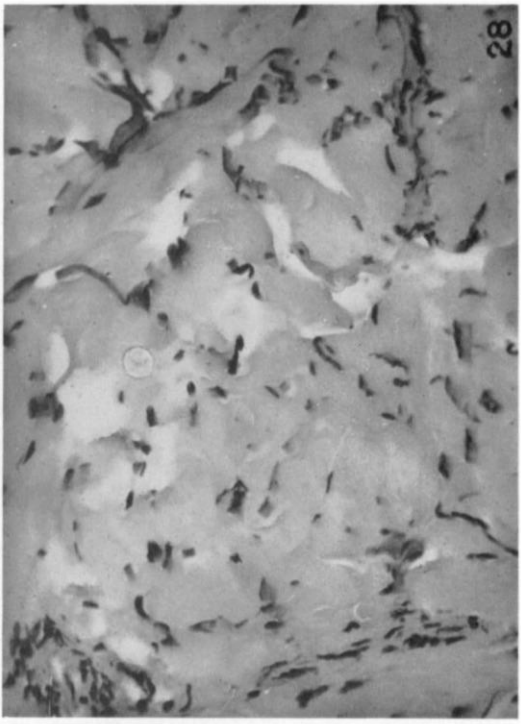
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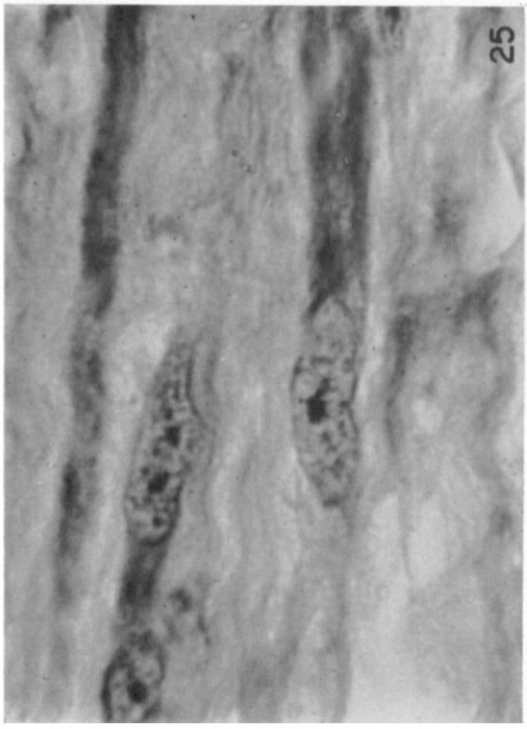
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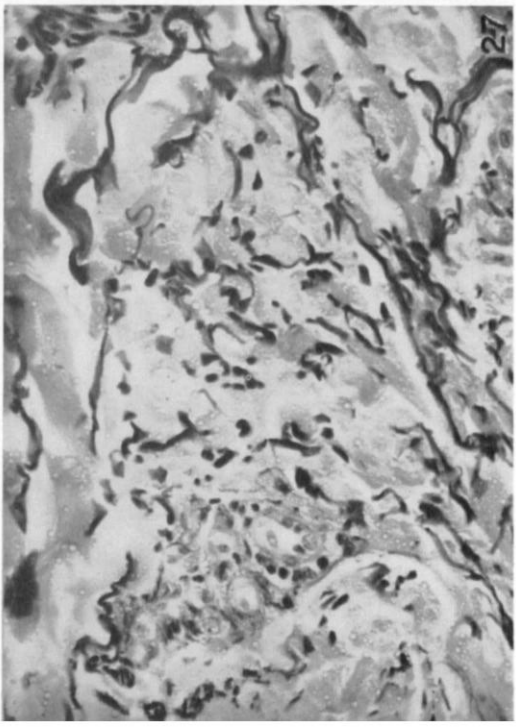

27

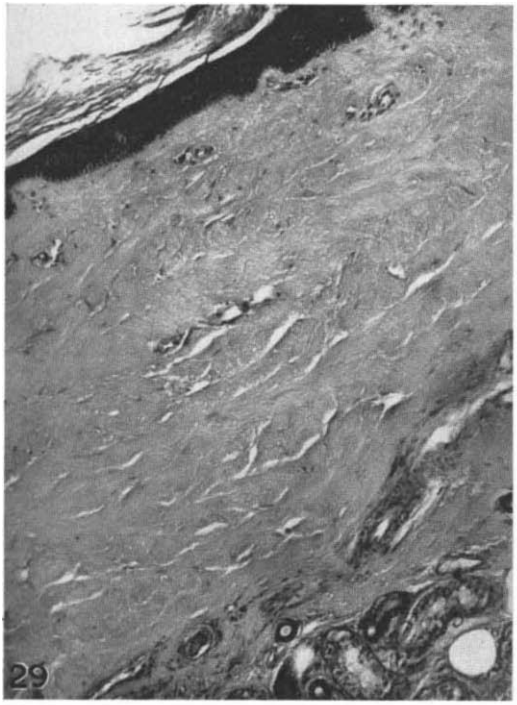
PLATE 7

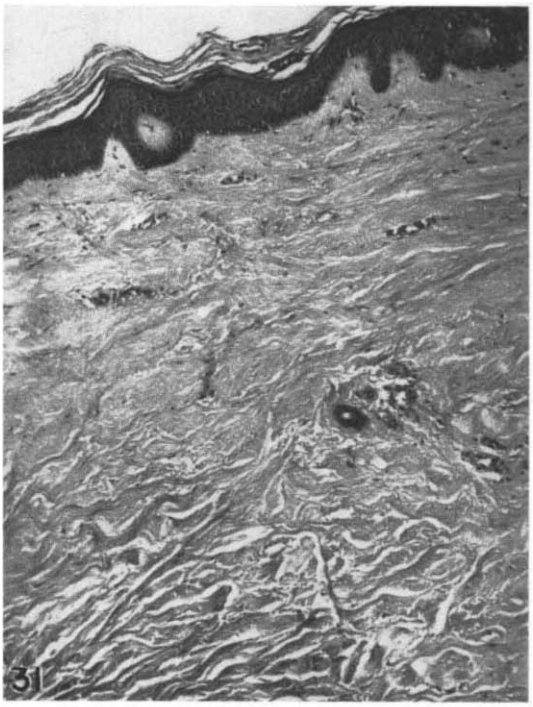
FIG. 29. Skin of diffuse sclerodermia before treatment with prednisone showing fibrosis and hyalinization of collagen fibers and bundles in all layers of connective tissue. Hematoxylin-eosine. × 96.

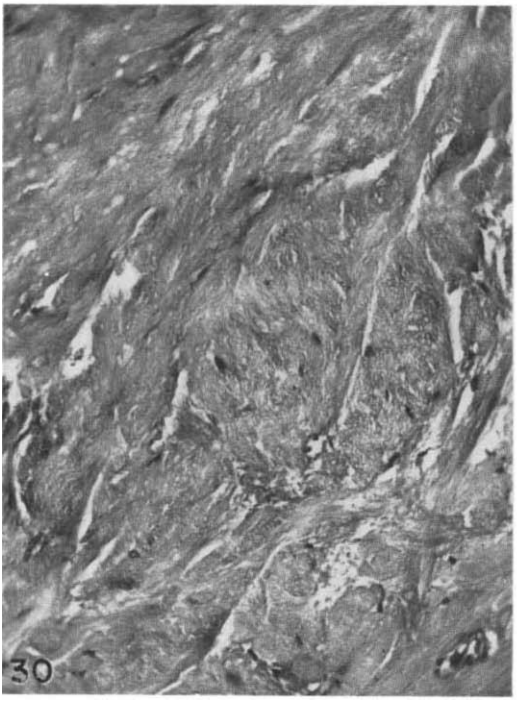
FIG. 30. Middle chorium of the same case at high magnification. Hematoxylin-eosine. × 191.

FIG. 31. The same case after four week treatment with prednisone (30 mg dayly). Separation and slight dissotiation of collagen bundles predominantly in the middle and deep chorium. Hematoxylin-eosin, × 96.

FIG. 32. Middle chorium of the same case after treatment at high magnification. Dissotiation of collagen bundles, reduction of hyalinization and less number of fibroblasts. Hematoxylin-eosine. × 191.







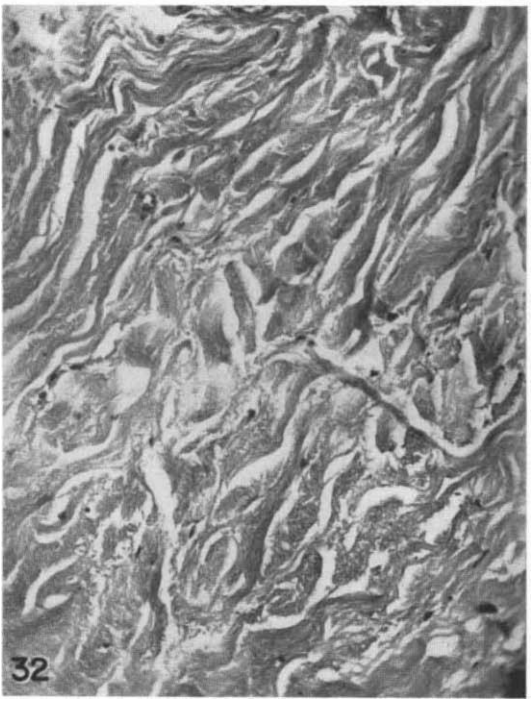


PLATE 7

PLATE 8

FIG. 33. Moderate thick basal membrane of preceding case of sclerodermia before treatment. PAS-hematoxylin stain. × 609.

FIG. 34. Basal membrane of the same case after treatment with prednisone. No appreciable change is seen. PAS-hematoxylin. × 609.

FIG. 35. Thick and short elastic fibers of the middle chorium of the preceding case of sclerodermia before treatment. Orcein stain. × 348.

FIG. 36. Slight fragmentation of elastic fibers in the same case after treatment with prednisone. Orcein stain. × 348.

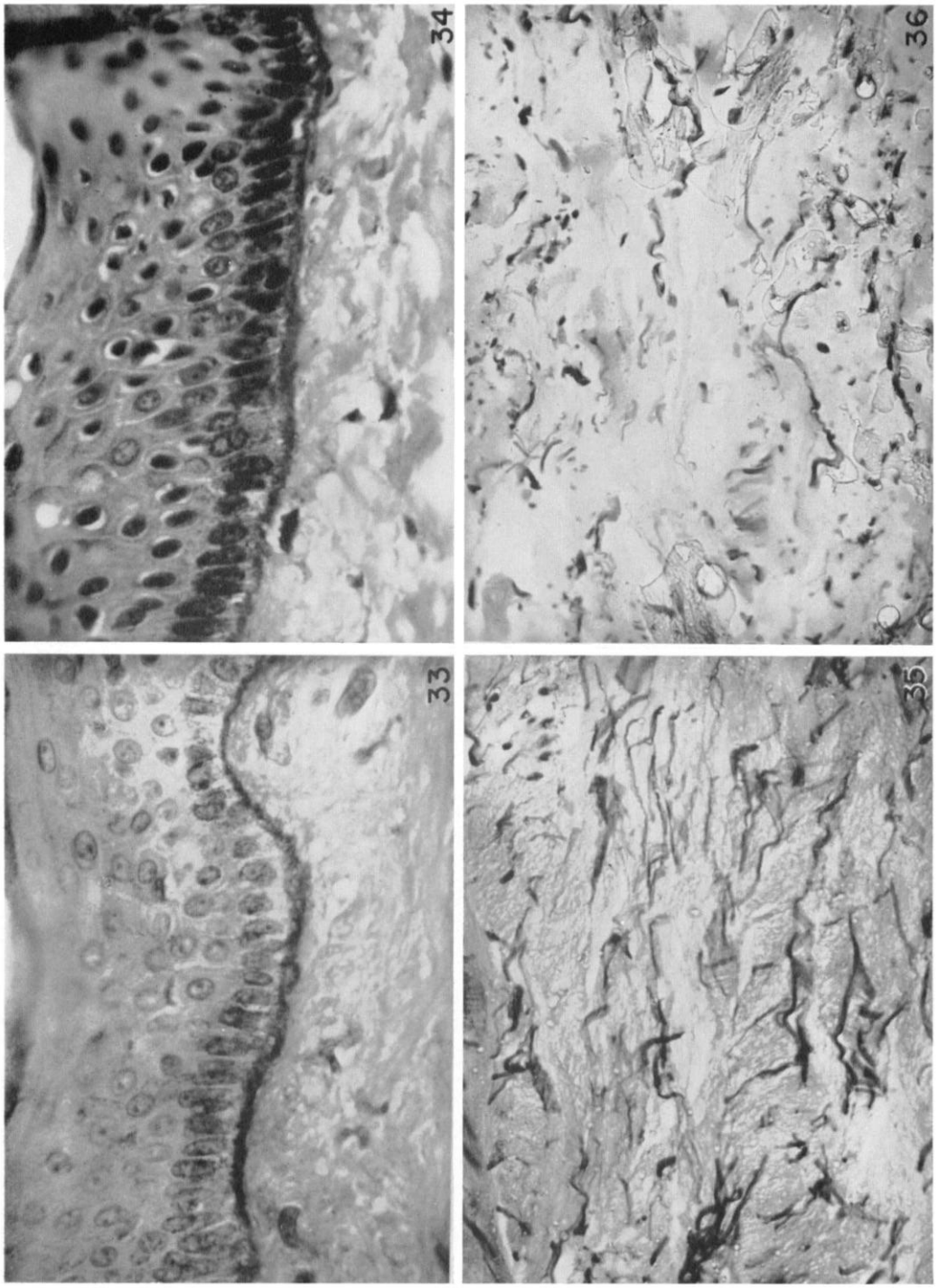


PLATE 1